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FILE COVERS 1907 - 2 Dec 2004  VOL 141 ISS 23
FILE LAST UPDATED: 1 Dec 2004  (20041201/ED)

 This file contains CAS Registry Numbers for easy and accurate
 substance identification.

'OBI' IS DEFAULT SEARCH FIELD FOR 'HCAPLUS' FILE

=> d que l7
L4   (        43) SEA FILE=HCAPLUS ABB=ON  PLU=ON  ("DRUZGALA P"/AU OR "DRUZGALA
                  PASCAL"/AU OR "DRUZGALA PASCAL J"/AU OR "DRUZGALA PASCAL
                  JEAN"/AU)
L5   (        65) SEA FILE=HCAPLUS ABB=ON  PLU=ON  "MILNER P"/AU OR ("MILNER
                  PETER G"/AU OR "MILNER PETER GERARD"/AU)
L6   (       270) SEA FILE=HCAPLUS ABB=ON  PLU=ON  PFISTER J?/AU
L7             6 SEA FILE=HCAPLUS ABB=ON  PLU=ON  L4 AND L5 AND L6


=> d all l7 1-6

L7   ANSWER 1 OF 6  HCAPLUS  COPYRIGHT 2004 ACS on STN
AN   2003:1007850  HCAPLUS
DN   140:42168
ED   Entered STN:  28 Dec 2003
TI   Preparation of thiazolidinedione compounds for the treatment of diabetes,
     hyperlipidemia, hypercholesterolemia, and atherosclerosis
IN   Druzgala, Pascal; Milner, Peter G.; Pfister, Jurg
     R.
PA   USA
SO   U.S. Pat. Appl. Publ., 89 pp., Cont.-in-part of U.S. Pat. Appl. 2003
     54,974.
     CODEN: USXXCO
DT   Patent
LA   English
IC   ICM  C07J001-00
     ICS  A61K031-69; C07J043-00; C07J017-00; A61K031-58
NCL  514064000; 514176000; 514172000; 540004000; 540107000; 540116000
CC   28-7 (Heterocyclic Compounds (More Than One Hetero Atom))
     Section cross-reference(s): 1, 34, 63
FAN.CNT 5
     PATENT NO.          KIND   DATE        APPLICATION NO.        DATE
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PI	US 2003236227	A1	20031225	US 2002-251522	20020920
	US 2003064972	A1	20030403	US 2001-841351	20010424
	US 6680387	B2	20040120		
	US 2002045620	A1	20020418	US 2001-961538	20010921
	US 6784199	B2	20040831		
	US 2003027798	A1	20030206	US 2001-961542	20010921
	US 6768008	B2	20040727		
	US 2003054974	A1	20030320	US 2002-228670	20020826
PRAI	US 2001-841351	A2	20010424		
	US 2001-961538	A2	20010921		
	US 2001-961542	A2	20010921		
	US 2002-228670	A2	20020826		
	US 2000-199146P	P	20000424		
	US 2000-234423P	P	20000921		
	US 2001-281982P	P	20010406		
	US 2001-314792P	P	20010824		

CLASS

PATENT NO.	CLASS	PATENT FAMILY CLASSIFICATION CODES
US 2003236227	ICM	C07J001-00
	ICS	A61K031-69; C07J043-00; C07J017-00; A61K031-58
	NCL	514064000; 514176000; 514172000; 540004000; 540107000; 540116000
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US 2003027798 ECLA C07D417/14+333B+277B+263B; C07D417/14+333B+277B+277B C07D261/12; C07D277/20C; C07D277/34; C07D311/70; C07D413/04+263B+207; C07D413/12+263+261; C07D417/04+277B+207; C07D417/12+277B+207; C07D417/12+277B+213; C07D417/12+277B263; C07D417/12+277B+263B; C07D417/12+307+277B; C07D417/12+311C+277B; C07D417/14+277+263B+213; C07D417/14+277B+213+207; C07D417/14+277B+263+207; C07D417/14+277B+263B+213; C07D417/14+277B+263B241B; C07D417/14+277B+263B+261; C07D417/14+277B+277B+207; C07D417/14+277B+277B+261; C07D417/14+07+277B+207; C07D417/14+311C+277B+207; C07D417/14+333B+277B+263B; C07D417/14+333B+277B+277B;

OS MARPAT 140:42168

GI

* STRUCTURE DIAGRAM TOO LARGE FOR DISPLAY - AVAILABLE VIA OFFLINE PRINT *

AB The subject invention provides pharmaceutical compds. useful in the treatment of Type II diabetes. Thiazolidinedione derivs., e.g. I (R = OH, CO2H, Q, Q1, etc., R1 = R2 = H, R1R2 = double bond), II (R3 = Ph, 4-FC6H4, 4-MeOC6H4, 3-methyl-2-thienyl, 2-pyridyl, etc., R4, R5 = H, Me, R6 = R7 = R8 = H, Z = O, S; R6R7 = double bond, R8 = Me), III, IV (R6 = R7 = H, Y = Q2, Q3, Q4, etc.; R6R7 = double bond, Y = 2-benzothiazolyl, 2-pyridyl, Q2, etc.), etc., were prepared to be tested as agents for treating diabetes, hyperlipidemia, hypercholesterolemia, and atherosclerosis. Thus, (R)-6-hydroxy-2,5,7,8-tetramethylchroman-2-carboxylic acid reacted with 5-(4-hydroxybenzylidene)thiazolidine-2,4-dione in CH2Cl2/THF using DCC/DMAP to give 5-{4-[(R)-6-hydroxy-2,5,7,8-tetramethylchroman-2-carboxy]benzylidene}thiazolidine-2,4-dione. These compds. are advantageous because they are readily metabolized by the metabolic drug detoxification systems. Particularly, thiazolidinedione analogs that have been designed to include esters within the structure of the compds. are provided.

ST thiazolidinedione prepn diabetes mellitus hypercholesterolemia hyperlipidemia atherosclerosis treatment; type II diabetes thiazolidinedione

IT Antiarteriosclerotics
(antiatherosclerotics; preparation of thiazolidinedione compds. for treatment of diabetes mellitus, hyperlipidemia, hypercholesterolemia, and atherosclerosis)

IT Lipids, biological studies
RL: BSU (Biological study, unclassified); BIOL (Biological study)
(hyperlipidemia; preparation of thiazolidinedione compds. for treatment of diabetes mellitus, hyperlipidemia, hypercholesterolemia, and atherosclerosis)

IT Antidiabetic agents
Diabetes mellitus
(non-insulin-dependent; preparation of thiazolidinedione compds. for treatment of diabetes mellitus, hyperlipidemia, hypercholesterolemia, and atherosclerosis)

IT Anticholesteremic agents
Atherosclerosis
Hypercholesterolemia
Hypolipemic agents

(preparation of thiazolidinedione compds. for treatment of diabetes mellitus, hyperlipidemia, hypercholesterolemia, and atherosclerosis)

IT 371244-62-1P 635315-22-9P 635315-23-0P
RL: PAC (Pharmacological activity); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)
(preparation of thiazolidinedione compds. for treatment of diabetes mellitus, hyperlipidemia, hypercholesterolemia, and atherosclerosis)

IT 96-33-3, Methyl acrylate 100-07-2, 4-Methoxybenzoyl chloride 104-94-9, p-Anisidine 109-09-1, 2-Chloropyridine 109-83-1, 2-(Methylamino)ethanol 123-08-0, 4-Hydroxybenzaldehyde 147-85-3, (L)-Proline, reactions 344-25-2, (D)-Proline 615-18-9, 2-Chlorobenzoxazole 615-20-3, 2-Chlorobenzothiazole 1571-08-0, Methyl 4-formylbenzoate 2133-40-6, (L)-Proline methyl ester hydrochloride 2295-31-0, 2,4-Thiazolidinedione 3581-91-7, 4,5-Dimethylthiazole 5680-80-8, L-Serine methyl ester hydrochloride 20207-16-3, Ethyl 2-aminoacetoacetate hydrochloride 23356-96-9, (S)-2-Pyrrolidinemethanol 39994-75-7, L-Threonine methyl ester hydrochloride 65365-28-8, (D)-Proline methyl ester hydrochloride 68832-13-3, (R)-2-Pyrrolidinemethanol 69427-83-4 163180-79-8 371244-64-3 371249-66-0, (R)-6-Hydroxy-2,5,7,8-tetramethylchroman-2-carboxylic acid 371249-71-7, (S)-6-Hydroxy-2,5,7,8-tetramethylchroman-2-carboxylic acid
RL: RCT (Reactant); RACT (Reactant or reagent)
(preparation of thiazolidinedione compds. for treatment of diabetes mellitus, hyperlipidemia, hypercholesterolemia, and atherosclerosis)

IT 20989-42-8P, N-Benzoyl-L-serine methyl ester 66552-11-2P 73594-87-3P 74772-78-4P, 5-(4-Hydroxybenzyl)thiazolidine-2,4-dione 79893-89-3P, N-Benzoyl-L-threonine methyl ester 148834-02-0P, (S)-1-(2-Benzoxazolyl)-2-hydroxymethylpyrrolidine 184840-77-5P, 5-(4-Methoxybenzyl)thiazolidine-2,4-dione 195603-76-0P 199167-77-6P 371244-49-4P 371244-51-8P, (S)-N-(2-Benzoxazolyl)proline 371244-53-0P 494870-55-2P 494870-61-0P 494870-62-1P
RL: RCT (Reactant); SPN (Synthetic preparation); PREP (Preparation); RACT (Reactant or reagent)
(preparation of thiazolidinedione compds. for treatment of diabetes mellitus, hyperlipidemia, hypercholesterolemia, and atherosclerosis)

IT 78715-83-0P, Methyl (S)-2-phenyl-2-oxazoline-4-carboxylate 88336-08-7P 103788-60-9P 122320-77-8P 122321-04-4P 124811-87-6P 148833-98-1P, (S)-1-(2-Benzothiazolyl)-2-(hydroxymethyl)pyrrolidine 199167-79-8P 371244-42-7P 371244-50-7P 371244-52-9P, (R)-N-(2-Benzoxazolyl)proline 371244-63-2P 371244-65-4P 494870-54-1P 494870-63-2P 494870-64-3P 635315-30-9P 635315-31-0P 635315-32-1P 635315-33-2P 635315-34-3P 635315-35-4P
RL: SPN (Synthetic preparation); PREP (Preparation)
(preparation of thiazolidinedione compds. for treatment of diabetes mellitus, hyperlipidemia, hypercholesterolemia, and atherosclerosis)

L7 ANSWER 2 OF 6 HCAPLUS COPYRIGHT 2004 ACS on STN
AN 2003:301058 HCAPLUS
DN 138:297661
ED Entered STN: 18 Apr 2003
TI Mibefradil-based compounds as calcium channel blockers useful in the treatment of hypertension and angina
IN **Druzgala, Pascal; Milner, Peter G.; Pfister, Jurg R.**; Zhang, Xiaoming
PA Aryx Therapeutics, USA
SO PCT Int. Appl., 50 pp.
CODEN: PIXXD2

DT Patent
LA English
IC ICM C07D235-08
ICS C07C211-43; C07C233-08; C07C317-14; A61K031-415
CC 1-8 (Pharmacology)
FAN.CNT 1

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PI	WO 2003031415	A1	20030417	WO 2002-US32562	20021010
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	US 2003130330	A1	20030710	US 2002-269139	20021010
	US 6608097	B2	20030819		
	EP 1438297	A1	20040721	EP 2002-773743	20021010
	R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO, MK, CY, AL, TR, BG, CZ, EE, SK				
	US 2004034237	A1	20040219	US 2003-643699	20030818
PRAI	US 2001-328588P	P	20011010		
	US 2002-269139	A1	20021010		
	WO 2002-US32562	W	20021010		

CLASS

PATENT NO.	CLASS	PATENT FAMILY CLASSIFICATION CODES
WO 2003031415	ICM	C07D235-08
	ICS	C07C211-43; C07C233-08; C07C317-14; A61K031-415
US 2004034237	ECLA	C07D235/14

OS MARPAT 138:297661
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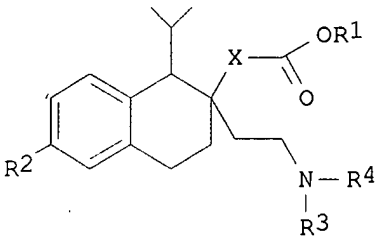

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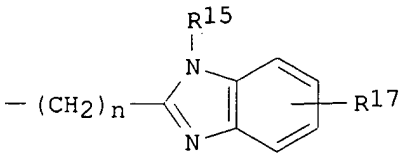

II

AB The invention provides mibefradil-based calcium channel blockers I [X = bond, (CH2)n, O, S, O(CH2)n (n = 1-6); R1 = C1-6 alkyl, optionally substituted with OH or NH2; R2 = F, COOR5 (R5 = R1); R3 = CH3, (CH2)nCOOR6, (n = 1-6; R6 = R1); R4 = (CH2)nCOR7R8, (CH2)nR10R11, Q1; R7 = O, NH, NR9, R8 = optionally substituted aryl or heterocyclyl; R9 = C1-6 alkyl; R10 = O, S, SO, SO2, NH, NR12, N(CH2)mCOOR13; R11 = aryl or heterocyclyl optionally substituted with (CH2)nCOOR14, R12-R14 = R1; R15 = (CH2)n COOR16, R16 = R1; R17 = absent or COOR18; R18 = R1; n = 1-6] useful in the treatment of hypertension, angina pectoris, ischemia, arrhythmias and cardiac insufficiency.

ST mibefradil deriv calcium channel blocker therapeutic; hypertension mibefradil deriv calcium channel blocker; angina mibefradil deriv calcium channel blocker; ischemia mibefradil deriv calcium channel blocker; arrhythmia mibefradil deriv calcium channel blocker; cardiac insufficiency mibefradil deriv calcium channel blocker

IT Heart, disease
(angina pectoris; mibefradil-based compds. as calcium channel blockers for treatment of hypertension and angina)

IT Heart, disease
(arrhythmia; mibefradil-based compds. as calcium channel blockers for treatment of hypertension and angina)

IT Ion channel blockers
(calcium; mibefradil-based compds. as calcium channel blockers for treatment of hypertension and angina)

IT Heart, disease
(failure; mibefradil-based compds. as calcium channel blockers for treatment of hypertension and angina)

IT Liver
(liver function test; mibefradil-based compds. as calcium channel blockers for treatment of hypertension and angina)

IT Enzymes, biological studies
RL: BSU (Biological study, unclassified); BIOL (Biological study)
(metabolic, non-oxidative; mibefradil-based compds. as calcium channel blockers for treatment of hypertension and angina)

IT Drug interactions
(metabolic; mibefradil-based compds. as calcium channel blockers for treatment of hypertension and angina)

IT Anti-ischemic agents
Antiarrhythmics
Antihypertensives
Cardiovascular agents
Drug delivery systems
Drug metabolism
Human
Hypertension
Ischemia
Pharmacokinetics
(mibefradil-based compds. as calcium channel blockers for treatment of hypertension and angina)

IT 9027-41-2, Hydrolase 9035-51-2, Cytochrome P 450, biological studies
RL: BSU (Biological study, unclassified); BIOL (Biological study)
(mibefradil-based compds. as calcium channel blockers for treatment of hypertension and angina)

IT 116644-53-2D, Mibefradil, derivs.
RL: PAC (Pharmacological activity); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(mibefradil-based compds. as calcium channel blockers for treatment of

hypertension and angina)
RE.CNT 4 THERE ARE 4 CITED REFERENCES AVAILABLE FOR THIS RECORD
RE
(1) Anon; PATENT ABSTRACTS OF JAPAN 1999, V1999(05)
(2) Branca, Q; US 4808605 A 1989 HCAPLUS
(3) Hoffmann La Roche; EP 0524512 A 1993 HCAPLUS
(4) Nippon Kayaku Co Ltd; JP 11035483 A 1999 HCAPLUS

L7 ANSWER 3 OF 6 HCAPLUS COPYRIGHT 2004 ACS on STN
AN 2003:242312 HCAPLUS
DN 138:271671
ED Entered STN: 28 Mar 2003
TI Preparation of pharmaceutical compounds including thiazolidinediones for the treatment of diabetes, hyperlipidemia, hypercholesterolemia, and atherosclerosis
IN **Druzgala, Pascal; Milner, Peter G.; Pfister, Jurg R.**
PA Aryx Therapeutics, USA
SO PCT Int. Appl., 162 pp.
CODEN: PIXXD2
DT Patent
LA English
IC ICM C07D277-34
ICS A61K031-425; C07D277-20; C07D417-12; C07D417-14; A61P003-10
CC 28-7 (Heterocyclic Compounds (More Than One Hetero Atom))
Section cross-reference(s): 1, 34, 63
FAN.CNT 5

	PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
PI	WO 2003024943	A2	20030327	WO 2002-US30017	20020920
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	US 6680387	B2	20040120		
	US 2002045620	A1	20020418	US 2001-961538	20010921
	US 6784199	B2	20040831		
	US 2003027798	A1	20030206	US 2001-961542	20010921
	US 6768008	B2	20040727		
	WO 2003017946	A2	20030306	WO 2002-US27298	20020826
	WO 2003017946	A3	20031120		
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CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG

US 2003054974	A1	20030320	US 2002-228670	20020826	
EP 1425030	A2	20040609	EP 2002-768732	20020826	
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PRAI US 2000-199146P	P	20000424			
US 2000-234423P	P	20000921			
US 2001-281982P	P	20010406			
US 2001-841351	A	20010424			
US 2001-297838P	P	20010613			
US 2001-314792P	P	20010824			
US 2001-961538	A2	20010921			
US 2001-961542	A2	20010921			
US 2002-228670	A2	20020826			
WO 2002-US27298	W	20020826			
WO 2002-US30017	W	20020920			

CLASS

PATENT NO.	CLASS	PATENT FAMILY CLASSIFICATION CODES
WO 2003024943	ICM	C07D277-34
	ICS	A61K031-425; C07D277-20; C07D417-12; C07D417-14; A61P003-10
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US 2003027798	ECLA	C07D261/12; C07D277/20C; C07D277/34; C07D311/70; C07D413/04+263B+207; C07D413/12+263+261; C07D417/04+277B+207; C07D417/12+277B+207; C07D417/12+277B+213; C07D417/12+277B263; C07D417/12+277B+263B; C07D417/12+307+277B; C07D417/12+311C+277B; C07D417/14+277+263B+213; C07D417/14+277B+213+207; C07D417/14+277B+263+207; C07D417/14+277B+263B+213; C07D417/14+277B+263B241B; C07D417/14+277B+263B+261; C07D417/14+277B+277B+207; C07D417/14+277B+277B+261; C07D417/14+07+277B+207;

C07D417/14+311C+277B+207; C07D417/14+333B+277B+263B;
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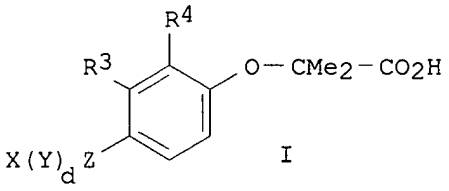
OS MARPAT 138:271671
GI



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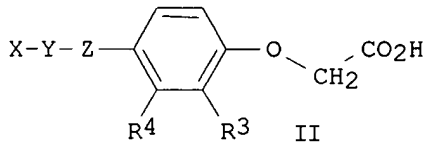

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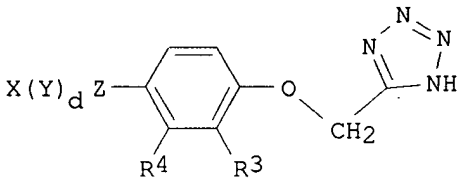

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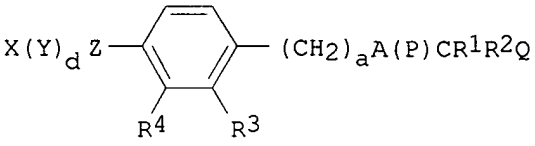

IV

AB The subject invention provides pharmaceutical compds. (I, II, III and IV; variables defined below; e.g. 1-(2-benzoxazolyl)-L-proline 4-[(2,4-dioxo-5-thiazolidinyl)methyl]phenyl ester (V), 1-(2-benzoxazolyl)-L-proline 4-[(2,4-dioxo-5-thiazolidinylidene)methyl]phe nyl ester (VI) and 4-[(2,4-dioxo-5-thiazolidinylidene)methyl]-, [(2S)-1-(2-benzoxazolyl)-2-pyrrolidinyl]methyl benzoate (VII)) useful in the treatment of Type II diabetes. These compds. are advantageous because they are readily metabolized by the metabolic drug detoxification systems. Particularly, thiazolidinedione analogs that have been designed to include esters within the structure of the compds. are provided. This invention also provides methods of treating disorders, such as diabetes, comprising the administration of therapeutically effective compns. comprising compds. that were designed to be metabolized by serum or intracellular hydrolases and esterases. Pharmaceutical compns. of the ester-containing thiazolidinedione analogs are also provided. Although the methods of preparation are not claimed, 40 example prepns. of intermediates and drug candidates are included; the examples are identical to those in WO 2001081328 (CAPLUS accession number 2001:798209). Percent reduction of serum glucose and insulin levels in mice having type II diabetes relative to the pretreatment values are shown for V, VI and VII. For I, II and III: R3 and R4 = H, CH3, CF3, OCH3, or halogen; d = 0 or 1; X = (un)substituted C3-8 cycloalkyl; (un)substituted phenyl; (un)substituted 5- or 6-membered heterocyclic ring containing at least 1, or optionally 2, or more heteroatoms such as O, S, or N; (un)substituted fused bicyclic ring containing a Ph ring fused with a 5- or 6-membered heterocyclic ring containing at least 1, or

optionally ≥2 heteroatoms such as O, N, or S. Y = pyrrolidine-1,2-diyl and 2-methylpyrrolidine-1,α-diyl enantiomers, -NMeCH2-, or -NMeCH2CH2- in which the N atom is attached to X and in which the 2-position of the pyrrolidine ring is attached to Z, either directly or through a methylene group. Z = a group that can be enzymically hydrolyzed or reduced, said enzymic reduction or hydrolysis results in the cleaving of Z into 2 mol. fractions including moieties -O(C:O)-, -(C:O)O-, -(C:O)S-, -S(C:O)-, -O(C:O)O-, -S-S-, - O-P(O)(OC1-6alkyl)O-, -P(O)(OC1-6alkyl)O-, -N:N-, -(C:O)NH-, -NH(C:O)-, - NHSO2-, -SO2NH-, -SO3-, -O3S-, cholesteryl-O(C:O)O-, cholesteryl-O(C:O)-, androstane 17β-(C:O) wherein the androstane group can contain 1-4 double bonds and can be optionally substituted by 1 or 2 oxo groups, 1-4 halogen atoms, 1-4 hydroxy groups, or 1-4 Me groups; alternatively, Z can also = -C6H4OCMe2CO2-, -O(CH2)jCMe2CO2-, -(CH2)kCR14R15CO2- or -CH2CH2CH(OH)CH2CH(OH)CH2CO2-, wherein j and k = 0-4, and R14 and R15 = H or C1-3 alkyl. For IV: a = 0 to 4; P and Q = H or CH3, or P and Q form a bond, resulting in a double bond between A and the adjacent C atom; A = CH, N, O, or S; however, if A = O or S, then P is absent and Q = H or CH3. R1 and R2 are linked and together form a chain having a length of 4- or 5-atoms, said chain containing at least 1 to 3 heteroatoms from the group O, S, or N, and said chain optionally containing at least 1 or 2-carbonyl (C:O) groups. Or R1 and R2 are not linked, and R1 can be -(C:O)NH2, -(C:O)OH, tetrazole, or -(C:O)O-C1-6 alkyl; and R2 can be a H atom; C1-3 alkyl; C1-6-alkoxy; C0-3 alkylenephenyl, wherein the Ph ring may be, optionally, substituted by ≥1 halogen atoms; tetrazole ring; (C:O)OH; (C:O)O-C1-6 alkyl; (C:O)bNR5R6, wherein b = 0 or 1. R5 = H or C1-6 alkyl, and R6 = H or B(C:O)cDR7 or B(CHOH)cDR7, where c = 0 or 1, B = a bond, a C1-6 alkylene, a C2-6 alkenylene, a C4-6 cycloalkenylene, a Ph optionally substituted by ≥1 C1-3 alkyl groups and/or ≥1 halogen atoms, or a 5- or 6-membered heterocyclic group containing at least 1 or optionally 2 heteroatoms, including any combination of O, N, or S at any position. D = a bond, a C1-3 alkyleneoxy, -O-, -NH-, or -N(C1-3 alkyl)-, R7 = C1-6 alkyl, C4-6 cycloalkyl or cycloalkenyl, Ph optionally substituted by ≥1 halogen atoms, C1-3 alkyl, C1-3 alkoxy, C0-3 alkyleneNR8R9 (each of R8 and R9 = H, C1-3 alkyl, SO2C1-3-alkyl, (C:O)OC1-3alkyl, SO2NHC1-3alkyl), C0-3alkyleneCOOH, C0-3alkylene(C:O)OC1-3alkyl, OCH2(C:O)NH2, a 5- or 6-membered heterocyclic ring containing at least 1 or optionally 2 heteroatoms, and including any combination of O, N, or S at any position, or a fused bicyclic ring containing a benzene ring fused with a 5- or 6-membered heterocyclic ring containing at least 1 heteroatom, including O, N, or S at any position, and optionally substituted by an oxo (:O) group, wherein said bicyclic fused ring can be attached to D via a ring atom of the heterocyclic ring either directly or through a C1-6 alkylene ER10, where E = O, S, or -NR11-; R10 and R11 = H or C1-3 alkyl. The rest of the variables are the same as for I-III.

ST thiazolidinedione analog prepn antidiabetic anticholesteremic hypolipemic antiatherosclerotic agent

IT Antiarteriosclerotics
(antiatherosclerotics; preparation of pharmaceutical compds. including thiazolidinedione analogs for treating diabetes, hypercholesterolemia, and atherosclerosis)

IT Lipids, biological studies
RL: BSU (Biological study, unclassified); BIOL (Biological study)
(hyperlipidemia; preparation of pharmaceutical compds. including thiazolidinedione analogs for treating diabetes, hypercholesterolemia, and atherosclerosis)

IT Diabetes mellitus
(non-insulin-dependent; preparation of pharmaceutical compds. including

thiazolidinedione analogs for treating diabetes, hypercholesterolemia, and atherosclerosis)

IT Anticholesteremic agents
Antidiabetic agents
Atherosclerosis
Hypercholesterolemia
Hypolipemic agents
(preparation of pharmaceutical compds. including thiazolidinedione analogs for treating diabetes, hypercholesterolemia, and atherosclerosis)

IT 148834-02-0P 195603-76-0P 199167-79-8P
RL: PAC (Pharmacological activity); RCT (Reactant); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); RACT (Reactant or reagent); USES (Uses)
(preparation of pharmaceutical compds. including thiazolidinedione analogs for treating diabetes, hypercholesterolemia, and atherosclerosis)

IT 74772-78-4P 78715-83-0P 88336-08-7P 122320-77-8P 122321-04-4P
124811-87-6P 148833-98-1P 371244-42-7P 371244-47-2P 371244-48-3P
371244-50-7P 371244-52-9P 371244-54-1P 371244-55-2P 371244-56-3P
371244-57-4P 371244-58-5P 371244-59-6P 371244-60-9P 371244-61-0P
371244-62-1P 371244-63-2P 371244-65-4P 371244-66-5P 371244-67-6P
371244-68-7P
RL: PAC (Pharmacological activity); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)
(preparation of pharmaceutical compds. including thiazolidinedione analogs for treating diabetes, hypercholesterolemia, and atherosclerosis)

IT 96-33-3, Methyl acrylate 98-88-4, Benzoyl chloride 100-07-2, 4-Methoxybenzoyl chloride 104-94-9, p-Anisidine 109-09-1, 2-Chloropyridine 109-83-1, 2-(Methylamino)ethanol 123-08-0, 4-Hydroxybenzaldehyde 147-85-3, (L)-Proline, reactions 344-25-2, (D)-Proline 615-18-9, 2-Chlorobenzoxazole 615-20-3, 2-Chlorobenzothiazole 1571-08-0, Methyl 4-formylbenzoate 2133-40-6, (L)-Proline methyl ester hydrochloride 2295-31-0, 2,4-Thiazolidinedione 3581-91-7, 4,5-Dimethylthiazole 5680-80-8, L-Serine methyl ester hydrochloride 20207-16-3, Ethyl 2-Aminoacetoacetate hydrochloride 23356-96-9 39994-75-7, L-Threonine methyl ester hydrochloride 65365-28-8, (D)-Proline methyl ester hydrochloride 68832-13-3 371244-43-8 371244-45-0 371244-51-8, N-2-Benzoxazolyl-L-proline 371244-64-3 371249-66-0, (R)-6-Hydroxy-2,5,7,8-tetramethylchroman-2-carboxylic acid 371249-71-7, (S)-6-Hydroxy-2,5,7,8-tetramethylchroman-2-carboxylic acid
RL: RCT (Reactant); RACT (Reactant or reagent)
(preparation of pharmaceutical compds. including thiazolidinedione analogs for treating diabetes, hypercholesterolemia, and atherosclerosis)

IT 20989-42-8P, N-Benzoyl-L-serine methyl ester 66552-11-2P 73594-87-3P 79893-89-3P 103788-60-9P 184840-77-5P 199167-77-6P 371244-44-9P 371244-46-1P 371244-49-4P 371244-53-0P
RL: RCT (Reactant); SPN (Synthetic preparation); PREP (Preparation); RACT (Reactant or reagent)
(preparation of pharmaceutical compds. including thiazolidinedione analogs for treating diabetes, hypercholesterolemia, and atherosclerosis)

L7 ANSWER 4 OF 6 HCAPLUS COPYRIGHT 2004 ACS on STN
AN 2003:97993 HCAPLUS
DN 138:153526
ED Entered STN: 07 Feb 2003
TI preparation of benzylazolidinediones for the treatment of diabetes, hyperlipidemia, hypercholesterolemia, and atherosclerosis

IN **Druzgala, Pascal; Milner, Peter G.; Pfister, Jurg R.**
PA Aryx Therapeutics, USA
SO U.S. Pat. Appl. Publ., 71 pp., Cont.-in-part of U.S. Ser. No. 841,351.
CODEN: USXXCO
DT Patent
LA English
IC ICM A61K031-675
ICS A61K031-53; A61K031-506; A61K031-501; A61K031-497; A61K031-4439; A61K031-426; A61K031-421; A61K031-4166
NCL 514084000; 514085000; 514092000; 514241000; 514252050; 514255050; 514340000; 514341000; 514369000; 514376000
CC 28-7 (Heterocyclic Compounds (More Than One Hetero Atom))
Section cross-reference(s): 1
FAN.CNT 5

	PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
PI	US 2003027798	A1	20030206	US 2001-961542	20010921
	US 6768008	B2	20040727		
	US 2003064972	A1	20030403	US 2001-841351	20010424
	US 6680387	B2	20040120		
	WO 2003017946	A2	20030306	WO 2002-US27298	20020826
	WO 2003017946	A3	20031120		
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	WO 2003024943	A3	20030522		
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	US 2001-281982P	P	20010406		
	US 2001-841351	A2	20010424		
	US 2001-314792P	P	20010824		
	US 2001-297838P	P	20010613		

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US 2001-961538	A2	20010921
US 2001-961542	A2	20010921
US 2002-228670	A2	20020826
WO 2002-US27298	W	20020826
WO 2002-US30017	W	20020920

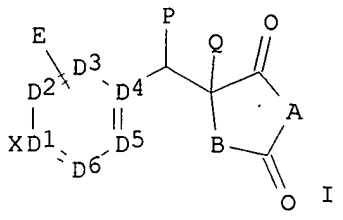
CLASS

PATENT NO.	CLASS	PATENT FAMILY CLASSIFICATION CODES
US 2003027798	ICM	A61K031-675
	ICS	A61K031-53; A61K031-506; A61K031-501; A61K031-497; A61K031-4439; A61K031-426; A61K031-421; A61K031-4166
	NCL	514084000; 514085000; 514092000; 514241000; 514252050; 514255050; 514340000; 514341000; 514369000; 514376000
US 2003027798	ECLA	C07D261/12; C07D277/20C; C07D277/34; C07D311/70; C07D413/04+263B+207; C07D413/12+263+261; C07D417/04+277B+207; C07D417/12+277B+207; C07D417/12+277B+213; C07D417/12+277B263; C07D417/12+277B+263B; C07D417/12+307+277B; C07D417/12+311C+277B; C07D417/14+277+263B+213; C07D417/14+277B+213+207; C07D417/14+277B+263+207; C07D417/14+277B+263B+213; C07D417/14+277B+263B241B; C07D417/14+277B+263B+261; C07D417/14+277B+277B+207; C07D417/14+277B+277B+261; C07D417/14+07+277B+207; C07D417/14+311C+277B+207; C07D417/14+333B+277B+263B; C07D417/14+333B+277B+277B;
US 2003064972	ECLA	C07D261/12; C07D277/20C; C07D277/34; C07D311/70; C07D413/04+263B+207; C07D413/12+263B+261; C07D417/04+277B+207; C07D417/12+277B+263B; C07D417/12+277B+263; C07D417/12+277+213; C07D417/12+277B+207; C07D417/12+307+277B; C07D417/12+311C+277B; C07D417/14+277B+277B+261; C07D417/14+277B+277B+207; C07D417/14+277B+263B+261; C07D417/14+277B+263B+241B; C07D417/14+277B+63B+213; C07D417/14+277B+263+207; C07D417/14+277B+213+207; C07D417/14+277+263B+213; C07D417/14+07+277B+207; C07D417/14+311C+277B+207; C07D417/14+333B+277B+263B; C07D417/14+333B+277B+277B;
US 2003236227	ECLA	C07D261/12; C07D277/20C; C07D277/34; C07D311/70; C07D413/04+263B+207; C07D413/12+263B+261; C07D417/04+277B+207; C07D417/12+277B+263B; C07D417/12+277B+263; C07D417/12+277+213; C07D417/12+277B+207; C07D417/12+307+277B; C07D417/12+311C+277B; C07D417/14+277B+277B+261; C07D417/14+277B+277B+207; C07D417/14+277B+263B+261; C07D417/14+277B+263B+241B; C07D417/14+277B+63B+213; C07D417/14+277B+263+207; C07D417/14+277B+213+207; C07D417/14+277+263B+213; C07D417/14+07+277B+207; C07D417/14+311C+277B+207; C07D417/14+333B+277B+263B; C07D417/14+333B+277B+277B

OS MARPAT 138:153526

GI

Searched by P. Ruppel



AB Title compds. [I; A, B = CH2, CO, N, NO, NH, S, SO, SO2, O; D1-D6 = CH, N, S, O; P, Q, E = H, (substituted) alkyl, CO2H, halo, OH, aryl, cyano, OH, NO2, NH2, etc.; PQ = double bond; X = OH, (substituted) CO2H], were prepared Thus, 4-hydroxybenzaldehyde, 2,4-thiazolidinedione, piperidine, and PhCO2H were stirred together in PhMe at 80° for 16 h to give 5-(4-hydroxybenzylidene)-2,4-thiazolidinedione. I at 10 mg/kg 2X/day in NIDDM mice gave a 36-40% reduction in serum glucose and a 9-13% reduction in serum insulin.

ST benzylazolidinedione prepn diabetes hyperlipidemia hypercholesterolemia atherosclerosis treatment; thiazolidinedione benzyl prepn diabetes hyperlipidemia hypercholesterolemia atherosclerosis treatment

IT Antiarteriosclerotics
(antiatherosclerotics; preparation of benzylazolidinediones for the treatment of diabetes, hyperlipidemia, hypercholesterolemia, and atherosclerosis)

IT Lipids, biological studies
RL: BSU (Biological study, unclassified); BIOL (Biological study)
(hyperlipidemia, treatment; preparation of benzylazolidinediones for the treatment of diabetes, hyperlipidemia, hypercholesterolemia, and atherosclerosis)

IT Diabetes mellitus
(non-insulin-dependent, treatment; preparation of benzylazolidinediones for the treatment of diabetes, hyperlipidemia, hypercholesterolemia, and atherosclerosis)

IT Anticholesteremic agents
Antidiabetic agents
Human
Hypolipemic agents
(preparation of benzylazolidinediones for the treatment of diabetes, hyperlipidemia, hypercholesterolemia, and atherosclerosis)

IT Atherosclerosis
Hypercholesterolemia
(treatment; preparation of benzylazolidinediones for the treatment of diabetes, hyperlipidemia, hypercholesterolemia, and atherosclerosis)

IT 103788-60-9P 195603-76-0P
RL: PAC (Pharmacological activity); RCT (Reactant); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); RACT (Reactant or reagent); USES (Uses)
(preparation of benzylazolidinediones for the treatment of diabetes, hyperlipidemia, hypercholesterolemia, and atherosclerosis)

IT 74772-78-4P 184840-77-5P 199167-77-6P 199167-79-8P 252357-90-7P 252357-91-8P 371244-53-0P 371244-62-1P 371244-63-2P 371244-65-4P 371244-66-5P 494870-54-1P 494870-55-2P 494870-56-3P 494870-57-4P 494870-58-5P 494870-59-6P
RL: PAC (Pharmacological activity); SPN (Synthetic preparation); THU

(Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)
(preparation of benzylazolidinediones for the treatment of diabetes, hyperlipidemia, hypercholesterolemia, and atherosclerosis)

IT 62-56-6, Thiourea, reactions 96-33-3, Methyl acrylate 98-88-4, Benzoyl chloride 100-07-2, 4-Methoxybenzoyl chloride 104-94-9, p-Anisidine 109-09-1, 2-Chloropyridine 109-83-1, 2-Methylaminoethanol 123-08-0, 4-Hydroxybenzaldehyde 147-85-3, L-Proline, reactions 344-25-2, D-Proline 615-18-9, 2-Chlorobenzoxazole 615-20-3, 2-Chlorobenzothiazole 1571-08-0, Methyl 4-formylbenzoate 2133-40-6, L-Proline methyl ester hydrochloride 2295-31-0, 2,4-Thiazolidinedione 3581-91-7, 4,5-Dimethylthiazole 5680-80-8, L-Serine methyl ester hydrochloride 20207-16-3, Ethyl 2-aminoacetoacetate hydrochloride 23356-96-9, (S)-2-Pyrrolidinemethanol 39994-75-7, L-Threonine methyl ester hydrochloride 53101-49-8 53174-06-4 65365-28-8 69427-83-4 163180-79-8 371244-64-3
RL: RCT (Reactant); RACT (Reactant or reagent)
(preparation of benzylazolidinediones for the treatment of diabetes, hyperlipidemia, hypercholesterolemia, and atherosclerosis)

IT 20989-42-8P 29450-04-2P 73594-87-3P 78715-83-0P 79893-89-3P 124811-87-6P 148833-98-1P 148834-02-0P 154005-98-8P 371244-42-7P 371244-49-4P 371244-50-7P 371244-51-8P 494870-60-9P 494870-61-0P 494870-62-1P 494870-63-2P 494870-64-3P 494870-65-4P
RL: RCT (Reactant); SPN (Synthetic preparation); PREP (Preparation); RACT (Reactant or reagent)
(preparation of benzylazolidinediones for the treatment of diabetes, hyperlipidemia, hypercholesterolemia, and atherosclerosis)

RE.CNT 46 THERE ARE 46 CITED REFERENCES AVAILABLE FOR THIS RECORD

RE

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(3) Anon; EP 0419035 A1 1991 HCAPLUS
(4) Anon; EP 0549365 A1 1993 HCAPLUS
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(13) Anon; EP 0953355 A1 1999 HCAPLUS
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L7 ANSWER 5 OF 6 HCAPLUS COPYRIGHT 2004 ACS on STN
AN 2001:903820 HCAPLUS
DN 136:15238
ED Entered STN: 14 Dec 2001
TI Materials and methods using cisapride analogs for the treatment of gastroesophageal reflux disease and other conditions
IN **Druzgala, Pascal; Milner, Peter G.; Pfister, Jurg**; Becker, Cyrus
PA Aryx Therapeutics, USA
SO PCT Int. Appl., 35 pp.
CODEN: PIXXD2
DT Patent
LA English
IC ICM A61K031-00
CC 1-9 (Pharmacology)
Section cross-reference(s): 27, 63
FAN.CNT 1

	PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
PI	WO 2001093849	A2	20011213	WO 2001-US18365	20010607
	WO 2001093849	A3	20030130		
	W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM				
	RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG				
	CA 2410939	AA	20011213	CA 2001-2410939	20010607
	US 2002025970	A1	20020228	US 2001-876698	20010607
	US 6552046	B2	20030422		
	EP 1296684	A2	20030402	EP 2001-942028	20010607
	R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO, MK, CY, AL, TR				

	JP 2003535128	T2	20031125	JP 2002-501422	20010607
	US 2003216387	A1	20031120	US 2003-418842	20030418
PRAI	US 2000-209926P	P	20000607		
	US 2001-876698	A1	20010607		
	WO 2001-US18365	W	20010607		

CLASS

PATENT NO.	CLASS	PATENT FAMILY CLASSIFICATION CODES
WO 2001093849	ICM	A61K031-00
US 2003216387	ECLA	A61K031/4468; C07D211/46; C07D211/58

OS MARPAT 136:15238

AB The invention provides compds. and compns. for the safe and effective treatment of gastroesophageal reflux and related conditions. In a preferred embodiment, the compns. of the subject invention comprise esterified cisapride derivs. These compns. possess potent activity in treating gastroesophageal reflux disease and substantially reduce adverse effects associated with the administration of cisapride. These adverse effects include, but are not limited to, diarrhea, abdominal cramping and elevations of blood pressure and heart rate. Also disclosed is a method using the compds. of the invention for treatment of a condition susceptible to treatment by modulation of serotoninergic systems.

ST gastroesophageal reflux disease cisapride analog prepn; serotoninergic therapeutic cisapride analog

IT Nervous system
(autonomic, disorders of control of autonomic function; cisapride analogs, and preparation thereof, for treatment of gastroesophageal reflux disease and other conditions)

IT Anti-Alzheimer's agents
Antidepressants
Antihypertensives
Antipsychotics
Anxiolytics
Cognition enhancers
Drug delivery systems
Dyspepsia
Gastrointestinal motility
Nervous system agents
Schizophrenia
(cisapride analogs, and preparation thereof, for treatment of gastroesophageal reflux disease and other conditions)

IT Intestine, disease
(constipation; cisapride analogs, and preparation thereof, for treatment of gastroesophageal reflux disease and other conditions)

IT Behavior
Sleep
(disorder; cisapride analogs, and preparation thereof, for treatment of gastroesophageal reflux disease and other conditions)

IT Toxicity
(drug; cisapride analogs, and preparation thereof, for treatment of gastroesophageal reflux disease and other conditions)

IT Hypertension
(essential; cisapride analogs, and preparation thereof, for treatment of gastroesophageal reflux disease and other conditions)

IT Digestive tract, disease
(gastroesophageal reflux; cisapride analogs, and preparation thereof, for treatment of gastroesophageal reflux disease and other conditions)

IT Drugs
(gastrointestinal; cisapride analogs, and preparation thereof, for treatment

of gastroesophageal reflux disease and other conditions)
IT Stomach, disease
(gastroparesis; cisapride analogs, and preparation thereof, for treatment of gastroesophageal reflux disease and other conditions)
IT Intestine, disease
(ileus, post-operative; cisapride analogs, and preparation thereof, for treatment of gastroesophageal reflux disease and other conditions)
IT Mental disorder
(mania; cisapride analogs, and preparation thereof, for treatment of gastroesophageal reflux disease and other conditions)
IT Mental disorder
(mood-affecting; cisapride analogs, and preparation thereof, for treatment of gastroesophageal reflux disease and other conditions)
IT Mental disorder
(obsession-compulsion; cisapride analogs, and preparation thereof, for treatment of gastroesophageal reflux disease and other conditions)
IT Surgery
(post-operative ileus; cisapride analogs, and preparation thereof, for treatment of gastroesophageal reflux disease and other conditions)
IT Intestine
(pseudo-obstruction; cisapride analogs, and preparation thereof, for treatment of gastroesophageal reflux disease and other conditions)
IT Psychotropics
(psychoactive substance use disorders; cisapride analogs, and preparation thereof, for treatment of gastroesophageal reflux disease and other conditions)
IT Nerve
(serotoninergic; cisapride analogs, and preparation thereof, for treatment of gastroesophageal reflux disease and other conditions)
IT 81098-60-4, Cisapride
RL: ADV (Adverse effect, including toxicity); BSU (Biological study, unclassified); BIOL (Biological study)
(cisapride analogs, and preparation thereof, for treatment of gastroesophageal reflux disease and other conditions)
IT 378781-04-5P 378781-05-6P 378781-06-7P
RL: PAC (Pharmacological activity); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)
(cisapride analogs, and preparation thereof, for treatment of gastroesophageal reflux disease and other conditions)
IT 81098-60-4D, Cisapride, analogs
RL: PAC (Pharmacological activity); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(cisapride analogs, and preparation thereof, for treatment of gastroesophageal reflux disease and other conditions)
IT 378781-03-4P
RL: RCT (Reactant); SPN (Synthetic preparation); PREP (Preparation); RACT (Reactant or reagent)
(preparation and reaction; cisapride analogs, and preparation thereof, for treatment of gastroesophageal reflux disease and other conditions)
IT 79-10-7, Acrylic acid, reactions 96-32-2, Bromoacetic acid methyl ester 2969-81-5, 4-Bromobutyric acid ethyl ester 83863-69-8
RL: RCT (Reactant); RACT (Reactant or reagent)
(reaction; cisapride analogs, and preparation thereof, for treatment of gastroesophageal reflux disease and other conditions)

L7 ANSWER 6 OF 6 HCAPLUS COPYRIGHT 2004 ACS on STN
AN 2001:798209 HCAPLUS

DN 135:344475
ED Entered STN: 02 Nov 2001
TI Preparation of pharmaceutical compounds including thiazolidinediones for the treatment of diabetes, hyperlipidemia, hypercholesterolemia, and atherosclerosis
IN **Druzgala, Pascal; Milner, Peter G.; Pfister, Jurg R.**
PA Aryx Therapeutics, USA
SO PCT Int. Appl., 100 pp.
CODEN: PIXXD2
DT Patent
LA English
IC ICM C07D277-34
ICS C07D417-12; C07D417-14; C07J003-00; A61K031-426; A61K031-427; A61K031-4439; A61K031-497; A61K031-56; A61P003-10
CC 28-7 (Heterocyclic Compounds (More Than One Hetero Atom))
Section cross-reference(s): 1, 34, 63
FAN.CNT 5

	PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
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	WO 2001081328	A3	20020221		
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	RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG				
	CA 2402123	AA	20011101	CA 2001-2402123	20010424
	EP 1276730	A2	20030122	EP 2001-932617	20010424
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	JP 2003531200	T2	20031021	JP 2001-578420	20010424
PRAI	US 2000-199146P	P	20000424		
	US 2001-281982P	P	20010406		
	WO 2001-US13131	W	20010424		

CLASS

PATENT NO.	CLASS	PATENT FAMILY CLASSIFICATION CODES
WO 2001081328	ICM	C07D277-34
	ICS	C07D417-12; C07D417-14; C07J003-00; A61K031-426; A61K031-427; A61K031-4439; A61K031-497; A61K031-56; A61P003-10

OS MARPAT 135:344475
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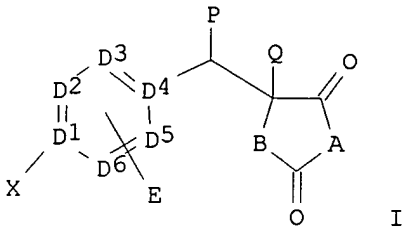

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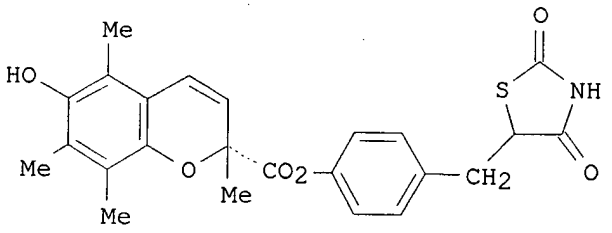

II

AB Pharmaceutical compds. I (A and B = same or different and are C, N, NO, NH, SO0-2, O; D1-D6 = same or different and are C, N, S, O; E = attached to one or more of D1-D6 atoms; P and Q = double bond or P, Q, E = same or different and are H, C1-10 (un)substituted alkyl, (un)substituted carboxylic esters, halogen, CO, OH, phosphate, phosphonate, aryl, CN, CO2H, NO2, NH2, SO2-4, C1-20 heteroalkyl, alkenyl, alkynyl, cycloalkyl and any may be substituted with C1-6 alkyl, halogen, OH, NH2, CN, NO2, CO2H, SO2-4; X = OH, CO2H or a substituted carboxylic group comprising O2C- or CO2- which is attached to D1) and their analogs, derivs., salts were prepared and are useful for the treatment of Type II diabetes; no data included. These compds., especially thiazolidinedione analogs designed as esters are advantageous because they are readily metabolized by the metabolic drug detoxification systems. Thus II was prepared from (R)-6-hydroxy-2,5,7,8-tetramethylchroman-2-carboxylic acid and 5-(4-hydroxybenzyl)thiazolidine-2,4-dione in methylene chloride and THF to which was added dicyclohexylcarbodiimide and DMAP.

ST thiazolidinedione analog prepn antidiabetic anticholesteremic hypolipemic antiatherosclerotic agent

IT Antiarteriosclerotics
(antiatherosclerotics; preparation of pharmaceutical compds. including thiazolidinedione analogs for treating diabetes, hypercholesterolemia, and atherosclerosis)

IT Anticholesteremic agents
Antidiabetic agents
Atherosclerosis
Hypercholesterolemia
Hypolipemic agents
(preparation of pharmaceutical compds. including thiazolidinedione analogs for treating diabetes, hypercholesterolemia, and atherosclerosis)

IT Heterocyclic compounds
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); RCT (Reactant); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); RACT (Reactant or reagent); USES (Uses)

Searched by P. Ruppel

(preparation of pharmaceutical compds. including thiazolidinedione analogs for treating diabetes, hypercholesterolemia, and atherosclerosis)

IT Diabetes mellitus
(type II; preparation of pharmaceutical compds. including thiazolidinedione analogs for treating diabetes, hypercholesterolemia, and atherosclerosis)

IT 148834-02-0P 195603-76-0P 199167-79-8P
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); RCT (Reactant); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); RACT (Reactant or reagent); USES (Uses)
(preparation of pharmaceutical compds. including thiazolidinedione analogs for treating diabetes, hypercholesterolemia, and atherosclerosis)

IT 74772-78-4P 78715-83-0P 88336-08-7P 122320-77-8P 122321-04-4P
124811-87-6P 148833-98-1P 371244-42-7P 371244-47-2P 371244-48-3P
371244-50-7P 371244-52-9P 371244-54-1P 371244-55-2P 371244-56-3P
371244-57-4P 371244-58-5P 371244-59-6P 371244-60-9P 371244-61-0P
371244-62-1P 371244-63-2P 371244-65-4P 371244-66-5P 371244-67-6P
371244-68-7P
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)
(preparation of pharmaceutical compds. including thiazolidinedione analogs for treating diabetes, hypercholesterolemia, and atherosclerosis)

IT 62-56-6, Thiourea, reactions 75-09-2, Methylene chloride, reactions
96-33-3, Methyl acrylate 98-88-4, Benzoyl chloride 100-07-2,
4-Methoxybenzoyl chloride 104-94-9, p-Anisidine 109-09-1,
2-Chloropyridine 109-83-1, 2-(Methylamino)ethanol 123-08-0,
4-Hydroxybenzaldehyde 147-85-3, (L)-Proline, reactions 344-25-2,
(D)-Proline 615-18-9, 2-Chlorobenzoxazole 615-20-3,
2-Chlorobenzothiazole 1571-08-0, Methyl 4-formylbenzoate 2133-40-6,
(L)-Proline methyl ester hydrochloride 2295-31-0, 2,4-Thiazolidinedione
3581-91-7, 4,5-Dimethylthiazole 5680-80-8, L-Serine methyl ester
hydrochloride 20207-16-3, Ethyl 2-Aminoacetoacetate hydrochloride
23356-96-9 39994-75-7, L-Threonine methyl ester hydrochloride
65365-28-8, (D)-Proline methyl ester hydrochloride 68832-13-3
371244-43-8 371244-45-0 371244-51-8, N-2-Benzoxazolyl-L-proline
371244-64-3 371249-66-0, (R)-6-Hydroxy-2,5,7,8-tetramethylchroman-2-carboxylic acid 371249-71-7, (S)-6-Hydroxy-2,5,7,8-tetramethylchroman-2-carboxylic acid
RL: RCT (Reactant); RACT (Reactant or reagent)
(preparation of pharmaceutical compds. including thiazolidinedione analogs for treating diabetes, hypercholesterolemia, and atherosclerosis)

IT 20989-42-8P, N-Benzoyl-L-serine methyl ester 66552-11-2P 73594-87-3P
79893-89-3P 103788-60-9P 184840-77-5P 199167-77-6P 371244-44-9P
371244-46-1P 371244-49-4P 371244-53-0P
RL: RCT (Reactant); SPN (Synthetic preparation); PREP (Preparation); RACT (Reactant or reagent)
(preparation of pharmaceutical compds. including thiazolidinedione analogs for treating diabetes, hypercholesterolemia, and atherosclerosis)

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DICTIONARY FILE UPDATES:  30 NOV 2004  HIGHEST RN 791034-84-9

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Experimental and calculated property data are now available. For more
information enter HELP PROP at an arrow prompt in the file or refer
to the file summary sheet on the web at:
http://www.cas.org/ONLINE/DBSS/registryss.html

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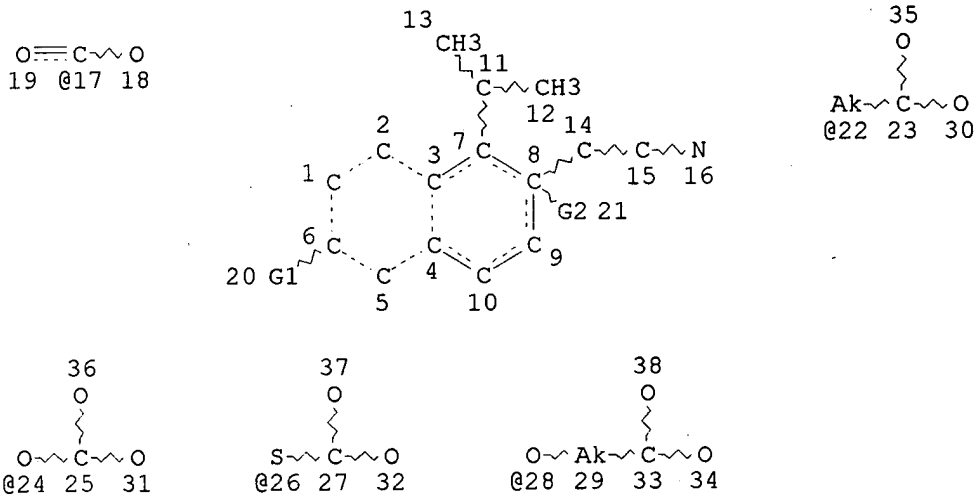


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CONNECT IS E1  RC AT  37
CONNECT IS E1  RC AT  38
DEFAULT MLEVEL IS ATOM
DEFAULT ECLEVEL IS LIMITED
ECOUNT  IS M1-X6 C  AT  22
ECOUNT  IS M1-X6 C  AT  29

GRAPH ATTRIBUTES:
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RING(S) ARE ISOLATED OR EMBEDDED
NUMBER OF NODES IS 38

STEREO ATTRIBUTES: NONE
L2 4 SEA FILE=REGISTRY SSS FUL L1

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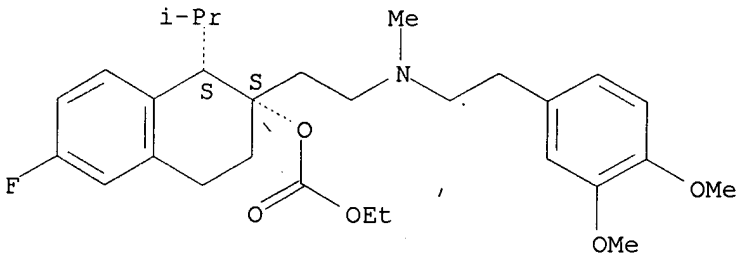
L2 ANSWER 1 OF 4 REGISTRY COPYRIGHT 2004 ACS on STN
RN 104221-42-3 REGISTRY
CN Carbonic acid, 2-[2-[[2-(3,4-dimethoxyphenyl)ethyl]methylamino]ethyl]-6-fluoro-1,2,3,4-tetrahydro-1-(1-methylethyl)-2-naphthalenyl ethyl ester, cis- (9CI) (CA INDEX NAME)
OTHER CA INDEX NAMES:
CN Carbonic acid, 2-[2-[[2-(3,4-dimethoxyphenyl)ethyl]methylamino]ethyl]-6-fluoro-1,2,3,4-tetrahydro-1-(1-methylethyl)-2-naphthalenyl ethyl ester, cis-(±)-
FS STEREOSEARCH
MF C29 H40 F N O5
CI COM
SR CA
LC STN Files: CA, CAPLUS, USPATFULL
DT.CA CAplus document type: Patent
RL.P Roles from patents: BIOL (Biological study); PREP (Preparation); USES (Uses)

Relative stereochemistry.



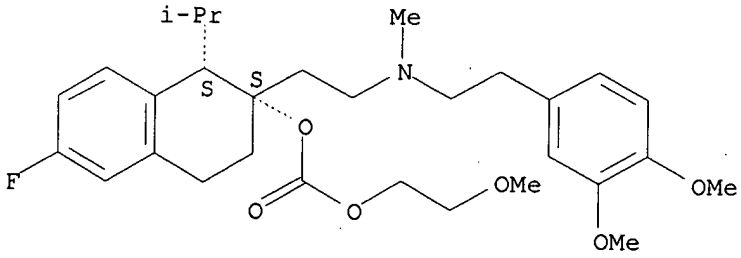
PROPERTY DATA AVAILABLE IN THE 'PROP' FORMAT

1 REFERENCES IN FILE CA (1907 TO DATE)
1 REFERENCES IN FILE CAPLUS (1907 TO DATE)

L2 ANSWER 2 OF 4 REGISTRY COPYRIGHT 2004 ACS on STN
RN 104205-37-0 REGISTRY
CN Carbonic acid, 2-[2-[[2-(3,4-dimethoxyphenyl)ethyl]methylamino]ethyl]-6-fluoro-1,2,3,4-tetrahydro-1-(1-methylethyl)-2-naphthalenyl 2-ethoxyethyl ester, cis- (9CI) (CA INDEX NAME)
OTHER CA INDEX NAMES:
CN Carbonic acid, 2-[2-[[2-(3,4-dimethoxyphenyl)ethyl]methylamino]ethyl]-6-fluoro-1,2,3,4-tetrahydro-1-(1-methylethyl)-2-naphthalenyl 2-ethoxyethyl ester, cis-(±)-
FS STEREOSEARCH
MF C30 H42 F N O6
CI COM

SR CA
LC STN Files: CA, CAPLUS, USPATFULL
DT.CA CAplus document type: Patent
RL.P Roles from patents: BIOL (Biological study); PREP (Preparation); USES (Uses)

Relative stereochemistry.



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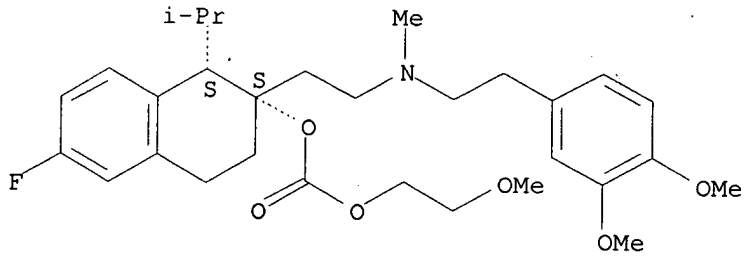
1 REFERENCES IN FILE CA (1907 TO DATE)
1 REFERENCES IN FILE CAPLUS (1907 TO DATE)

L2 ANSWER 3 OF 4 REGISTRY COPYRIGHT 2004 ACS on STN
RN 104205-36-9 REGISTRY
CN Carbonic acid, 2-[2-[[2-(3,4-dimethoxyphenyl)ethyl]methylamino]ethyl]-6-fluoro-1,2,3,4-tetrahydro-1-(1-methylethyl)-2-naphthalenyl 2-methoxyethyl ester, hydrochloride, cis- (9CI) (CA INDEX NAME)
OTHER CA INDEX NAMES:
CN Carbonic acid, 2-[2-[[2-(3,4-dimethoxyphenyl)ethyl]methylamino]ethyl]-6-fluoro-1,2,3,4-tetrahydro-1-(1-methylethyl)-2-naphthalenyl 2-methoxyethyl ester, hydrochloride, cis-(±)-
FS STEREOSEARCH
MF C30 H42 F N O6 . Cl H
SR CA
LC STN Files: CA, CAPLUS, USPATFULL
DT.CA CAplus document type: Patent
RL.P Roles from patents: BIOL (Biological study); PREP (Preparation); USES (Uses)
CRN (104205-37-0)

Relative stereochemistry.



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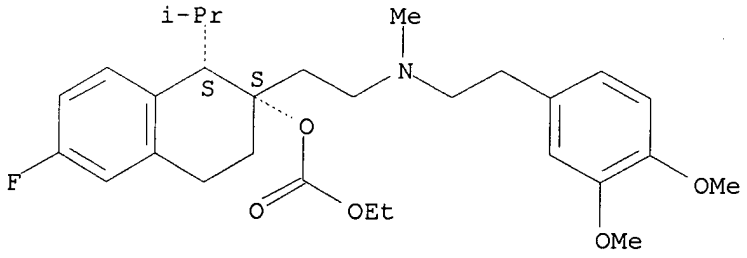
1 REFERENCES IN FILE CA (1907 TO DATE)
1 REFERENCES IN FILE CAPLUS (1907 TO DATE)

L2 ANSWER 4 OF 4 REGISTRY COPYRIGHT 2004 ACS on STN
RN 104205-35-8 REGISTRY
CN Carbonic acid, 2-[2-[[2-(3,4-dimethoxyphenyl)ethyl]methylamino]ethyl]-6-fluoro-1,2,3,4-tetrahydro-1-(1-methylethyl)-2-naphthalenyl ethyl ester, hydrochloride, cis- (9CI) (CA INDEX NAME)
OTHER CA INDEX NAMES:
CN Carbonic acid, 2-[2-[[2-(3,4-dimethoxyphenyl)ethyl]methylamino]ethyl]-6-fluoro-1,2,3,4-tetrahydro-1-(1-methylethyl)-2-naphthalenyl ethyl ester, hydrochloride, cis-(±)-
FS STEREOSEARCH
MF C29 H40 F N O5 . Cl H
SR CA
LC STN Files: CA, CAPLUS, USPATFULL
DT.CA CAplus document type: Patent
RL.P Roles from patents: BIOL (Biological study); PREP (Preparation); USES (Uses)
CRN (104221-42-3)

Relative stereochemistry.



● HCl

1 REFERENCES IN FILE CA (1907 TO DATE)
1 REFERENCES IN FILE CAPLUS (1907 TO DATE)

Searched by P. Ruppel

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FILE 'HCAPLUS' ENTERED AT 09:05:22 ON 02 DEC 2004
USE IS SUBJECT TO THE TERMS OF YOUR STN CUSTOMER AGREEMENT.
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FILE COVERS 1907 - 2 Dec 2004  VOL 141 ISS 23
FILE LAST UPDATED: 1 Dec 2004  (20041201/ED)

 This file contains CAS Registry Numbers for easy and accurate
 substance identification.

'OBI' IS DEFAULT SEARCH FIELD FOR 'HCAPLUS' FILE

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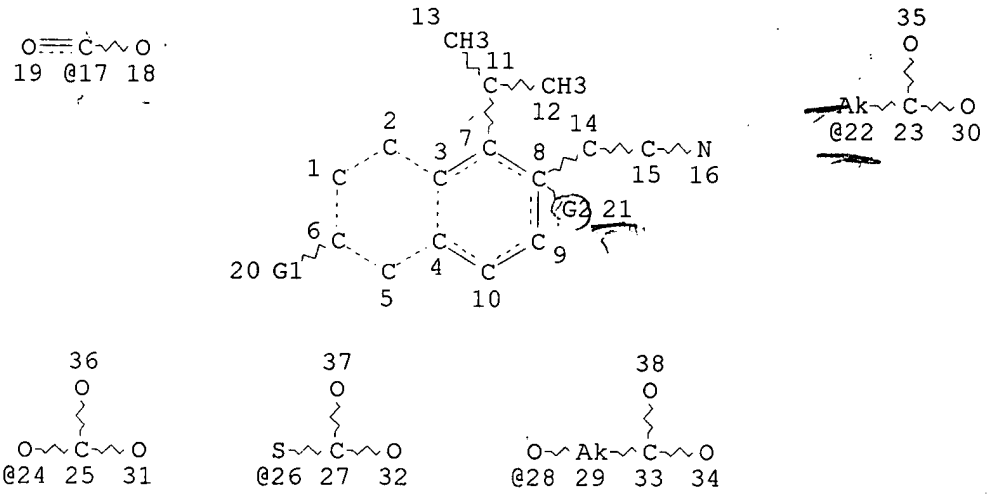


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1,604097

Searched by P. Ruppel

GRAPH ATTRIBUTES:
RING(S) ARE ISOLATED OR EMBEDDED
NUMBER OF NODES IS 38

STEREO ATTRIBUTES: NONE
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L3 1 SEA FILE=HCAPLUS ABB=ON PLU=ON L2

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L3 ANSWER 1 OF 1 HCAPLUS COPYRIGHT 2004 ACS on STN
AN 1987:49807 HCAPLUS
DN 106:49807
ED Entered STN: 21 Feb 1987
TI Tetrahydronaphthalene derivatives, their intermediates, and medicines containing them
IN Hengartner, Urs; Ramuz, Henri
PA Hoffmann-La Roche, F., und Co. A.-G., Fed. Rep. Ger.
SO Eur. Pat. Appl., 53 pp.
CODEN: EPXXDW
DT Patent
LA German
IC ICM C07C091-23
ICS C07C093-14; C07C093-00; C07C149-42; A61K031-135; A61K031-215
CC 25-24 (Benzene, Its Derivatives, and Condensed Benzenoid Compounds)
Section cross-reference(s): 1, 63
FAN.CNT 1

	PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
PI	EP 177960	A2	19860416	EP 1985-112863	19851010
	EP 177960	A3	19880113		
	EP 177960	B1	19910320		
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	FI 8503817	A	19860412	FI 1985-3817	19851002
	FI 83508	B	19910415		
	FI 83508	C	19910725		
	AU 8548301	A1	19860417	AU 1985-48301	19851004
	AU 589375	B2	19891012		
	ZA 8507681	A	19860528	ZA 1985-7681	19851004
	IL 76576	A1	19890131	IL 1985-76576	19851004
	JP 61091157	A2	19860509	JP 1985-222893	19851008
	HU 38605	A2	19860630	HU 1985-3915	19851009
	HU 199773	B	19900328		
	CN 85107496	A	19860723	CN 1985-107496	19851009
	CN 1007727	B	19900425		
	CA 1287636	A1	19910813	CA 1985-492588	19851009
	DK 8504648	A	19860412	DK 1985-4648	19851010
	NO 8504036	A	19860414	NO 1985-4036	19851010
	NO 161971	B	19890710		
	NO 161971	C	19891018		
	ES 547756	A1	19861116	ES 1985-547756	19851010
	US 4680310	A	19870714	US 1985-786253	19851010
	AT 61791	E	19910415	AT 1985-112863	19851010
	ES 554021	A1	19871216	ES 1986-554021	19860416
	ES 554020	A1	19880516	ES 1986-554020	19860416
PRAI	CH 1984-4870	A	19841011		
	EP 1985-112863	A	19851010		

CLASS

PATENT NO.	CLASS	PATENT FAMILY CLASSIFICATION CODES
EP 177960	ICM	C07C091-23
	ICS	C07C093-14; C07C093-00; C07C149-42; A61K031-135; A61K031-215

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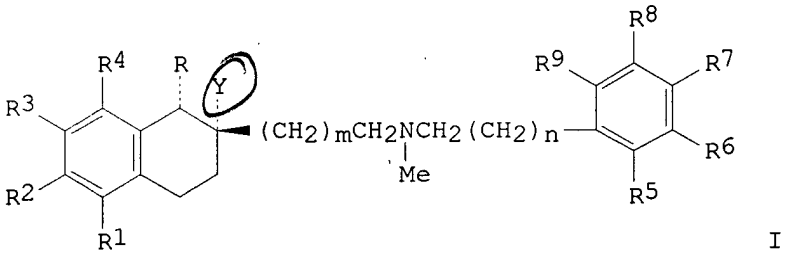

I

AB Tetrahydronaphthalene derivs. I [R = H, alkyl; R1-R4 = H, halo, alkoxy, etc.; R5-R9 = H, halo, C1-10 alkoxy, alkylthio, ω,ω,ω- trifluoroalkoxy, etc.; Y = OH, alkylcarbonyloxy, alkoxyalkylcarbonyloxy, alkoxycarbonyloxy, alkoxyalkoxycarbonyloxy, alkylthioalkylcarbonyloxy, (un)substituted benzylcarbonyloxy; m = 1, 2; n = 1, 2, 3] in racemates and optical antipodes, having Ca-antagonistic and antiarrhythmic effects, are prepared Thus, 2-(p-fluorphenyl)-3-methylbutyric acid was converted to the acid chloride and treated with ethylene in the presence of AlCl3 to give 6-fluoro-3,4-dihydro-1-isopropyl-2(1H)-naphthalenone, which underwent Grignard reaction with BrCH2CO2CMe3, followed by reduction with LiAlH4, to give 6-fluoro-1,2,3,4-tetrahydro-2-hydroxy-1α-isopropyl-2β-naphthalenylethanol. This intermediate was tosylated, condensed with N-methylhomoveratrylamine, and acylated with methoxyacetyl chloride to give 2-[2-[(3,4-dimethoxyphenylethyl)methylamino]ethyl]-6-fluoro-1,2,3,4-tetrahydro-1α-isopropyl-2α-naphthyl methoxyacetate-HCl (II). II was tested for Ca-antagonistic and hypotensive effects. A tablet was formulated containing II 75, lactose 135, starch 70, Povidone K 15, talc 3, and Mg stearate 2 mg.

ST naphthalene tetrahydro deriv prepn calcium antagonist; calcium antagonist tetrahydronaphthalene prepn; antiarrhythmic tetrahydronaphthalene deriv prepn; pharmaceutical tetrahydronaphthalene deriv prepn

IT Antiarrhythmics
Antihypertensives
(aralkylaminoalkyltetrahydronaphthalenes)

IT Ischemia
(treatment of, aralkylaminoalkyltetrahydronaphthalenes for)

IT Heart, disease or disorder
(angina pectoris, treatment of, aralkylaminoalkyltetrahydronaphthalenes for)

IT 37464-90-7
RL: RCT (Reactant); RACT (Reactant or reagent)
(Reformatsky reaction of, with Et bromoacetate)

IT 38870-89-2, Methoxyacetyl chloride
RL: RCT (Reactant); RACT (Reactant or reagent)
(acylation by, of naphthalenol derivative)

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IT 2472-13-1, 3,4-Dihydro-6,7-dimethoxy-2(1H)-naphthalenone
RL: RCT (Reactant); RACT (Reactant or reagent)
(alkylation of, with iso-Pr iodide)
IT 7440-70-2, biological studies
RL: BIOL (Biological study)
(antagonists, aralkylaminoalkyltetrahydronaphthalenes)
IT 3490-06-0, N-Methylhomoveratrylamine 104205-43-8
RL: RCT (Reactant); RACT (Reactant or reagent)
(condensation of, with naphthylethyl tosylate)
IT 51632-33-8
RL: PROC (Process)
(conversion of, to acid chloride)
IT 104204-91-3P
RL: RCT (Reactant); SPN (Synthetic preparation); PREP (Preparation); RACT (Reactant or reagent)
(preparation and Grignard reaction of, with tert-Bu bromoacetate)
IT 104204-98-0P
RL: RCT (Reactant); SPN (Synthetic preparation); PREP (Preparation); RACT (Reactant or reagent)
(preparation and Reformatsky reaction of, with Et bromoacetate)
IT 104204-89-9P 104205-42-7P 104205-73-4P
RL: RCT (Reactant); SPN (Synthetic preparation); PREP (Preparation); RACT (Reactant or reagent)
(preparation and condensation of, with amines)
IT 51631-55-1P
RL: RCT (Reactant); SPN (Synthetic preparation); PREP (Preparation); RACT (Reactant or reagent)
(preparation and cyclocondensation of, with ethylene)
IT 104204-93-5P
RL: RCT (Reactant); SPN (Synthetic preparation); PREP (Preparation); RACT (Reactant or reagent)
(preparation and dechlorination of)
IT 104205-02-9P
RL: RCT (Reactant); SPN (Synthetic preparation); PREP (Preparation); RACT (Reactant or reagent)
(preparation and hydrolysis of)
IT 104204-92-4P 104205-87-0P
RL: RCT (Reactant); SPN (Synthetic preparation); PREP (Preparation); RACT (Reactant or reagent)
(preparation and metal hydride reduction of)
IT 104205-03-0P 104205-79-0P
RL: RCT (Reactant); SPN (Synthetic preparation); PREP (Preparation); RACT (Reactant or reagent)
(preparation and reduction of)
IT 104205-85-8P
RL: RCT (Reactant); SPN (Synthetic preparation); PREP (Preparation); RACT (Reactant or reagent)
(preparation and reductive amination of)
IT 104204-90-2P 104205-78-9P
RL: RCT (Reactant); SPN (Synthetic preparation); PREP (Preparation); RACT (Reactant or reagent)
(preparation and tosylation of)
IT 104204-94-6P 104204-95-7P 104204-96-8P 104204-97-9P 104204-99-1P
104205-00-7P 104205-01-8P 104205-80-3P 104205-81-4P 104265-58-9P
104265-59-0P
RL: SPN (Synthetic preparation); PREP (Preparation)
(preparation of)
IT 104204-56-0P 104204-57-1P 104204-58-2P 104204-59-3P 104204-60-6P

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RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)
(preparation of, as calcium antagonist)

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